Scope and Limitations in Palladium-Catalyzed Substitution Reactions of Unsaturated Fused Lactones

Varinder K. Aggarwal,* Nuno Monteiro, Gary J. Tarver, and Ray McCague†

Department of Chemistry, University of Sheffield, Sheffield S3 7HF, England, and Chiroscience Ltd., Cambridge Science Park, Cambridge CB4 4WE, England

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The palladium-catalyzed nucleophilic substitution of C-4-substituted 2-oxabicyclo[3.3.0]oct-7-en-3-ones (unsaturated, fused lactones) have been studied particularly in relation to how electronic and steric factors influenced the rate and efficiency of substitution reactions. Thus, a range of α-substituted lactones were prepared (X = H, Me, OH, OAc, Br, N_3, NHCBZ) and subjected to palladium-catalyzed substitution reaction with diethyl sodiomalonate, and it was found that reaction rates increased with increasing electron-withdrawing ability of the substituent and that there was a strong correlation between rate and pK_a of the corresponding substituted acetic acids (XCH_2CO_2H). The only exception to the correlation was with X = OH, in which case the *endo* isomer reacted considerably faster than expected and the *exo* isomer reacted much slower than expected. It was also found that the rates of reaction of the *endo* isomers were greater than the *exo* isomers. The increased rates have been accounted for by a shift in equilibrium between the lactone and the π-allyl palladium intermediate toward the latter species due to the increased stability of the carboxylate (electronic effects) or relief of steric hindrance in the starting lactone. The scope and limitations of the palladium-catalyzed substitution reaction were studied by reacting a range of lactones with a range of nucleophiles. Lactones with unactivated leaving groups such as **2** (X = H) coupled efficiently with good nucleophiles such as malonate but only poorly with less reactive nucleophiles such as azide. Lactones with activated leaving groups such as **4a** (X = OH) coupled efficiently with a broad range of nucleophiles.

Introduction

Palladium-catalyzed substitution of allylic acetates is now a well-established and important process,[1,2] particularly because the π-allyl palladium complex can react with a large and still increasing number of nucleophiles. In addition, these reactions often proceed with high regio- and stereochemical control.[3] Net retention of configuration is observed in reactions involving soft nucleophiles, which attack the complex on the opposite face to the palladium. Hard nucleophiles attack palladium itself and furnish products with net inversion of stereochemistry. Regioselectivity is usually controlled by nonbonding steric interactions, and generally the nucleophile attacks the less hindered site.[4]

Most literature examples center around substitution reactions of allylic acetates. Unsaturated bicyclic lactones have also been studied as potential substrates for palladium-catalyzed substitution reactions, although most examples within this class have focused on *bridged* rather than the less strained *fused* lactones.[5] We recognized that bridged and fused lactones would show substantial differences in reactivity due to the differences in strain energy present in the two ring systems. Bridged lactones such as **1** should readily form π-allyl palladium intermediates, due to the relief of ring strain, and rapidly give substituted products (Scheme 1, eq 1). However, no strain is released upon reaction of the fused lactone (Scheme 1, eq 2), and so the π-allyl palladium species may react with its internal nucleophile, the carboxylate, and ring close again. Consequently, the π-allyl palladium intermediate is likely to be in equilibrium with the lactone. Indeed, there might only be a very low concentration of the π-allyl intermediate in the reaction mixture, in which case fused lactones would not be expected to readily undergo substitution reactions.

In fact, there was only one example of the use of a fused lactone (**2**) in a palladium-catalyzed substitution reaction, and this reaction had only been reported using the exceptionally good nucleophile dimethyl malonate.[6] This limited case together with the increasing availability of

* To whom correspondence should be addressed. E-mail: V.Aggarwal@Sheffield.ac.uk.

† Chiroscience Ltd.

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(1) For recent reviews on π-allyl palladium complexes see: Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257−276. Godlesky, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 585. Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089−1122. Heumann, A.; Réglier, M. *Tetrahedron* **1995**, *51*, 975−1015.

(2) Nucleophilic substitution of allylic acetates has also proved to be a particularly efficient method for the preparation of 1,4-*cis*-disubstituted cyclopent-2-enes. For general studies on palladium-mediated alkylation of cyclopentenyl acetates and related compounds see: Valpey, R, S.; Miller, D. J.; Estes, J. M.; Godleski, S. *J. Org. Chem.* **1982**, *47*, 4717−4720. Deardorff, D. R.; Linde, R. G., II; Martin, A. M.; Shulman, M. J. *J. Org. Chem.* **1989**, *54*, 2759−2762 and references cited therein. Gundersen, L. L.; Benneche, T.; Rise, F.; Gogoll, A.; Undheim, K. *Acta Chem. Scand.* **1992**, *46*, 761−771. Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327−9343. Shibasaki, M.; Nukui, S.; Mori, M. *Chem. Lett.* **1991**, 1791−1800.

(3) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1984**, *106*, 6837.

(4) For an exception see: Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297−6298 and references therein.

(5) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron. Lett.* **1979**, *20*, 2301−2304. Matsushita, H.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1982**, *1982*, 160−161. Negishi, E.; John, R. A. *J. Org. Chem.* **1983**, *48*, 4098−4102. Byström, S. E.; Aslanian, R.; Bäckvall, J. E. *Tetrahedron Lett.* **1985**, *26*, 1749−1752. Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143−1145. Tsuda, T.; Okada, M.; Nishi, S.; Seagusa, T. *J. Org. Chem.* **1986**, *51*, 421−426. Murahashi, S. I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292−3303. Tamaru, Y.; Tanaka, A.; Yasui, K.; Goto, S.; Tanaka, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 787−789. Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235−236.

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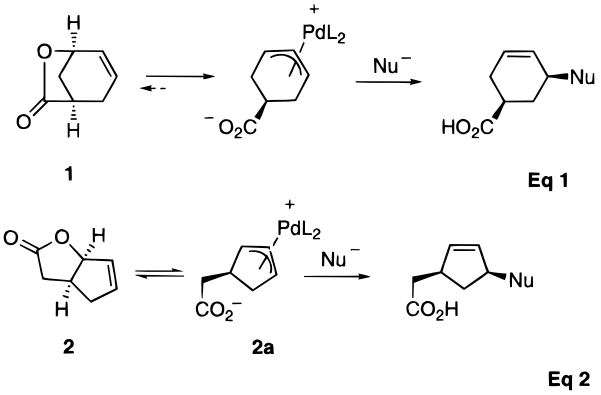
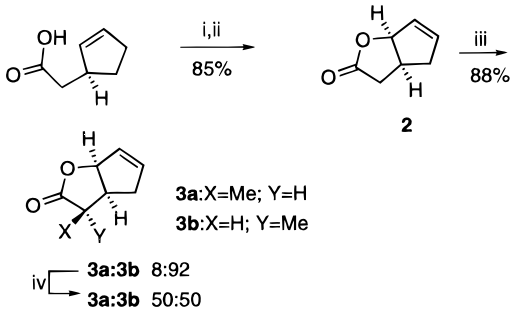
Scheme 1



Scheme 2[a]



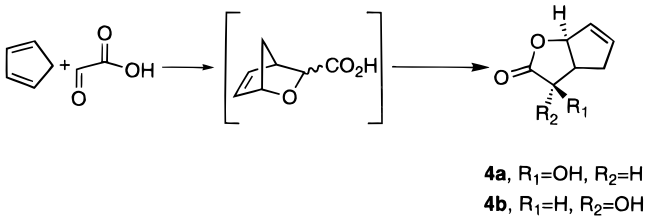
[a] Key: (i) I_2, KI, $NaHCO_3$, H_2O, rt; (ii) DBU, toluene, reflux; (iii) LDA, MeI, −78 °C; (iv) LDA, −78 °C then saturated Na_2SO_4.

enantiomerically pure lactones prompted us to embark on a study of palladium-catalyzed substitution reactions on fused lactones with a range of nucleophiles to explore the scope and limitations of this chemistry.[7] An advantage of substitution reactions of unsaturated lactones over allylic acetates is that they retain a charged carboxylate in the intermediate, and this would be expected to help control regiochemistry by charge/charge repulsion with the nucleophile. A further advantage with lactones is that, unlike allylic acetates, they cannot epimerize at the leaving group center, as the carboxylate intermediate cannot close to form a fused *trans* system.[8]

In this paper, we report on the synthesis of C-4-substituted 2-oxabicyclo[3.3.0]oct-7-en-3-ones and on their reactivity in palladium-mediated substitution reactions.

Preparation of the Lactones. We needed to prepare a broad range of C-4-substituted (H, Me, Br, N_3, NHCBZ, OAc) unsaturated lactones in order to probe steric and electronic effects in these reactions. The parent lactone **2**[9] was prepared as shown in Scheme 2 and was further transformed into the α-methyl lactones **3a** and **3b** by deprotonation using LDA followed by alkylation with iodomethane.[10] This gave an 8:92 ratio of *endo*:*exo* diastereomers (**3a**:**3b**) that were easily separable by chromatography. *Endo* diasteromer **3a** was obtained by equilibration of the mixture using LDA followed by quenching with saturated sodium sulfate.[11] This led to a 1:1 mixture of **3a**:**3b** from which the *endo* diastereomer **3a** was easily isolated in 40% yield.

Scheme 3



4a, R_1=OH, R_2=H
4b, R_1=H, R_2=OH

Hydroxy lactones **4a** and **4b** were prepared on a large scale by cycloaddition of glyoxylic acid and cyclopentadiene.[12] This furnished a 4:1 ratio of **4a**:**4b** in 30% yield (Scheme 3) from which **4a** was isolated by crystallization.

Lactone **4a** was a key intermediate in the synthesis of the remaining substituted lactones **6a**/**b**−**10a**/**b** used in this study. Thus, the *endo*-hydroxy lactone **4a** was converted into the corresponding *exo*-bromide **6b** (60% yield) by means of a modified Mitsonobu procedure using zinc bromide in combination with DEAD−triphenylphosphine.[13] The product was accompanied by 12% of its C-4 epimer (**6a**), which was separated by column chromatography. Displacement of bromide **6b** by azide afforded azido lactone **7a** (86%), which upon reduction[14] by triphenylphosphine in aqueous THF gave amino lactone **8a** (92%). This sequence allowed transformation of the hydroxy lactone into its amino derivative with overall retention of stereochemistry at C-4 and in 48% overall yield. Subsequent protection of **8a** gave the carbamate[15] **9a** (96%) (Scheme 4).

The C-4 epimers of compounds **7a**−**9a** (**7b**, **8b**, and **9b**, respectively) were prepared following the same procedures starting from the mesylate **5a**, Scheme 4. The *endo* and *exo* acetates **10a** and **10b**, respectively, were prepared by acylation of the corresponding alcohols.[12b]

Substitution Reactions. In 1980, Trost reported the palladium-catalyzed alkylation of unsubstituted lactone **2** with methyl sodiomalonate,[6] which gave **11** (Nu = $CH(CO_2Me)_2$) in good yield after 4 h in refluxing THF. We repeated this reaction and were surprised to find that the reaction was complete after only 5 min at room temperature. This was the first indication to us that in fact palladium-catalyzed substitution reactions of fused unsaturated lactones was a relatively facile process. We then attempted to use NaN_3 as nucleophile[16a−c] under similar conditions (room temperature, 24 h), but this gave an intractable mixture of four carboxylic acids (presum-

(6) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730−4743. Dimethyl sodiomalonate is often the nucleophile of choice when testing π-allyl palladium chemistry, presumably because it is highly reactive and adds irreversibly. Heteroatom nucleophiles *may* be more reactive than malonate, but they react reversibly. For an example, see: Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320−10321.

(7) For a preliminary account of this work see: Aggarwal, V. K.; Monteiro, N.; Tarver, G. J.; Lindell, S. D. *J. Org. Chem.* **1996**, *61*, 1192−1193.

(8) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, 2301−2304.

(9) Simple lactone see: Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298−5300 and references cited therein. For its preparation in optically pure form see: (a) *Via* norbornenone: Le Drian, C.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473−5483 and references cited therein. (b) *Via* iodo lactone: Troxler, T.; Scheffold, R. *Helv. Chim. Acta* **1994**, *77*, 1193−1202.

(10) Semmelhack, M. F.; Epa, W. R.; Cheung, A. W.-H.; Gu, Y.; Kim, C.; Zhang, N.; Lew, W. *J. Am. Chem. Soc.* **1994**, *116*, 7455−7456.

(11) Menges, M.; Bruckner, R. *Synlett* **1993**, 901−905 and references therein.

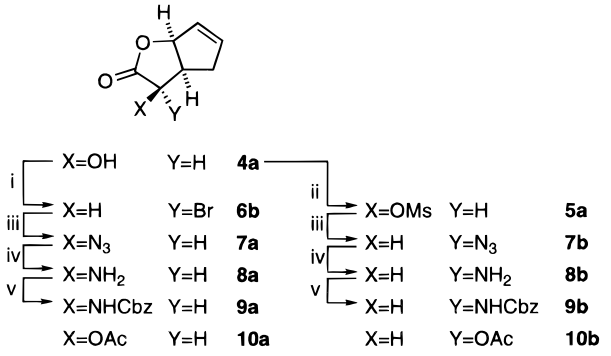
(12) (a) Lubineau, A.; Augé, J.; Grand, E.; Lubin, N. *Tetrahedron* **1994**, *50*, 10265−10276. (b) MacKeith, R. A.; McCague, R.; Olivo, H. F.; Roberts, S. M.; Taylor, S. J. C.; Xiong, H. *Bioorg. Med. Chem.* **1994**, 387−394. (c) Burlina, F.; Fourrey, J.-L.; Clivio, P.; Thomas, M. *Tetrahedron Lett.* **1994**, *35*, 8151−8152.

(13) Ho, P. T.; Davies, N. *J. Org. Chem.* **1984**, *49*, 3027−3029.

(14) Knouzi, N.; Vaultier, M.; Carrié, R. *Bull. Soc. Chim. Fr.* **1985**, 815−819.

(15) Fleet, G. W. J.; Chow, H.-F.; Bashyal, B. P. *Tetrahedron Lett.* **1986**, *27*, 3205−3208.

Scheme 4[a]

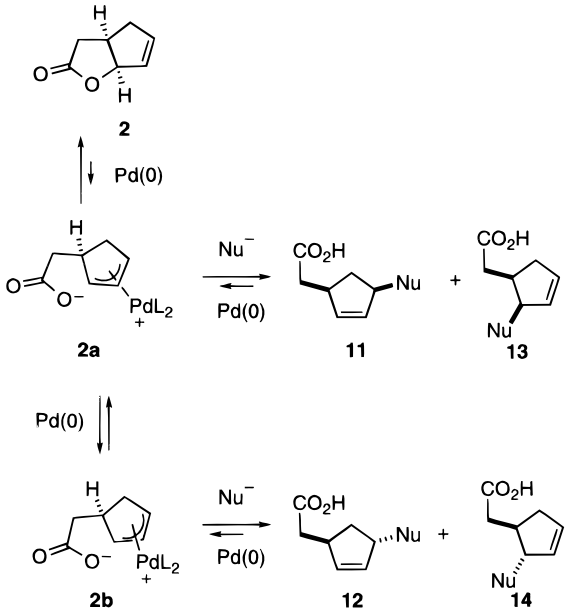


[a] Key: (i) $ZnBr_2$, PPh_3, DEAD, THF, rt; (ii) MsCl, Et_3N, DCM, 0 °C; (iii) NaN_3, DMSO, rt; (iv) PPh_3, THF−H_2O, rt; (v) $PhCH_2OCOCl$, $NaHCO_3$, THF−H_2O.

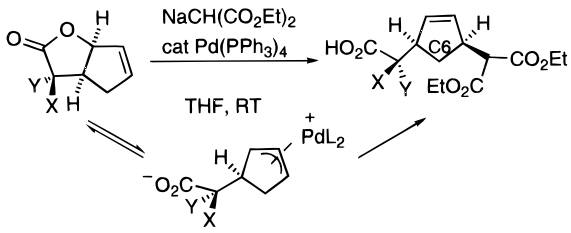
ably **11**−**14**) accompanied by 50% recovered starting material **2**. On the basis of our previous result using malonate, we were surprised to obtain a mixture of regio- and stereoisomers and substantial amounts of starting material.

The partial loss of stereochemistry in the process must be due to palladium mediated isomerization between *anti* and *syn* π-allyl palladium complexes **2a** and **2b** (Scheme 5).[16a,17] The formation of the two regioisomers could result from competitive azide attack adjacent rather than distal to the carboxylate or due to [3,3] sigmatropic rearrangement of the allyl azides.[16c] Proof that equilibration of the reaction was occurring was obtained by subjecting the mixture of azido acids **11**−**14** to the same reaction conditions as the initial reaction (this was achieved by treatment of **11**−**14** with NaH to form the corresponding carboxylate followed by treatment with $Pd(PPh_3)_4$ and NaN_3 in THF/H_2O). The products isolated were azido acids **11**−**14** (70%), obtained in the same ratio as above, and lactone **2** (30%). This proved not only that the reaction of azide with the palladium π-allyl intermediate was reversible but so too was its formation from the lactone. Reaction of **2** with $PhSO_2Na$ under refluxing conditions (no reaction being observed at room temperature) behaved similarly and gave mixtures of products together with recovered starting material. This indicated that nucleophiles that can also act as leaving groups are not suitable reagents for reaction with the unsubstituted

Scheme 5



Scheme 6



lactone **2**, due to equilibration between the π-allyl palladium intermediate and the lactone.

We reasoned that the position of the equilibrium between the unsaturated lactone and the π-allyl palladium complex could be influenced by substituents α to the carbonyl group due to both electronic and steric effects. An electron-withdrawing group at C-4 would favour ionization because not only would the carboxylate be a better leaving group but also because it would also be a poorer nucleophile. The presence of an *endo* substituent would also favor formation of the π-allyl palladium complex due to relief of ring strain. Thus, the effect of substitution at the C-4 position was investigated by reacting both *endo* and *exo* epimers of various lactones with ethyl sodiomalonate (Scheme 6) under palladium catalysis (Table 1).

Except in the special case of the *exo* hydroxy lactone **4b** (Table 1, entry 5), all lactones gave the corresponding carboxylic acid in good yield; pure compounds were obtained after a simple base−acid workup. The *exo*-hydroxy lactone **4b** led to a mixture of products from which we were able to isolate the desired product although in very poor yield; the byproducts have not been identified. We do not have an explanation for this anomalous reaction. The *cis* 1,4 relationship between the two substituents on the cyclopentene ring was assigned by ^1H NMR[7,19] and is based on the typical large difference in the chemical shift of the two diastereotopic protons at C-6 (Scheme 6).

Measurement of Reaction Rate. The effect of variation of the C-4 *endo* substituent on the rate of

(16) For studies on the reactivity of sodium azide toward π-allylpalladium complexes see: (a) Murahashi, S. I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292−3303. (b) Waegel, B.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 4851−4854. (c) Trost, B. M.; Pulley, S. R. *Tetrahedron Lett.* **1995**, *36*, 8737−8740.

(17) Deardorff, D. R.; Shulman, M. J.; Sheppeck, J. E., II. *Tetrahedron Lett.* **1989**, *30*, 6625−6628.

(18) Single (and different) diastereomers of bromo acids were obtained from the two lactones **6a** and **6b**, indicating that no epimerization had occurred. In the original studies, we found that the reaction of the *exo* bromo lactone (**6b**) with malonate gave rise to the same product as that obtained from the reaction of the *endo* bromo lactone (**6a**) with malonate. We believed that this was due to rapid epimerization of the two lactones followed by a slow palladium-catalyzed substitution reaction. The ratio of products obtained is dependent on the rates of the palladium-catalyzed substitution reactions (Curtin−Hammett); as *endo* isomers react at a faster rate than *exo* isomers only products derived from the *endo* isomer would be expected, and indeed, this was observed. However, in subsequent studies we have found that the rate of the palladium-catalyzed substitution reaction is strongly dependent on the quality of $Pd(PPh_3)_4$. Using freshly prepared catalyst, the palladium-catalyzed substitution reactions were significantly faster. In the case of the bromo lactones, the reactions with malonate were now so fast that there was essentially no time for equilibration at the bromide stereocenter of the two lactones, and each isomer reacted cleanly to give the corresponding substitution products.

(19) Sable, H. Z.; Ritchey, W. M.; Norlander, J. E. *Carbohydr. Res.* **1965**, *1*, 10−21. Wolczunowicz, G.; Bors, L.; Postenak, Th. *Helv. Chim. Acta* **1970**, *53*, 739−749.

Table 1. Reaction of Lactones with Ethyl Sodiomalonate[a]

entry	X	Y	lactone	yield (%)
1	H	H	**2**	93
2	Me	H	**3a**	87[b]
3	H	Me	**3b**	74[b]
4	OH	H	**4a**	87
5	H	OH	**4b**	15
6	Br	H	**6a**	77[c]
7	H	Br	**6b**	83[c]
8	N_3	H	**7a**	85
9	H	N_3	**7b**	86
10	NHCbz	H	**9a**	79
11	H	NHCbz	**9b**	76
12	OAc	H	**10a**	83
13	H	OAc	**10b**	72

[a] Reactions conducted on 1 mmol scale using 5 mol % $Pd(PPh_3)_4$ and 2 equiv of nucleophile at room temperature in THF. All yields refer to isolated pure materials. [b] Reaction conducted in refluxing THF. [c] See ref 18.

Table 2. Relative Reaction Rates of *endo*-Substituted Lactones[a]

entry	X	Y	lactone	k_{rel}	pK_a[b]
1	Me	H	**3a**	$\ll 1$[c]	4.87
2	H	H	**2**	1.0	4.74
3	OAc	H	**10a**	3.1	3.58
4	N_3	H	**7a**	8.9	3.03
5	Br	H	**6a**	11.6	2.86
6	OH	H	**4a**	>50[d]	3.83

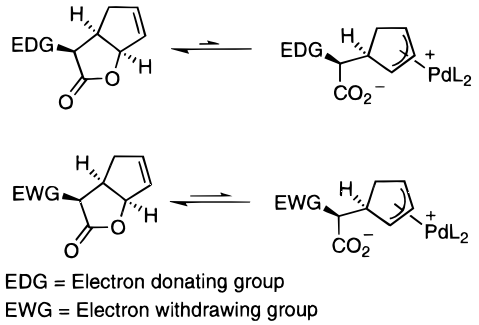
[a] Reactions were conducted at 0.125 M concentration in THF at rt using 1 mol % $Pd(PPh_3)_4$ and 2 equiv of ethyl sodiomalonate. Rates were determined by FTIR except for lactones **3a** and **7a**, which were determined by GC using a Chromopak CPSIL-8 column and helium as a carrier gas at 8 psi pressure. Ethyl cinnamate was used as internal standard in the case of **3a** and diethyl tartrate as internal standard for **7a**. All reactions were conducted using the same batch of $Pd(PPh_3)_4$, as different batches have different activity and so lead to different absolute rates. Relative rates are therefore more meaningful. The rate constant for entry **2** was found to be 6.4×10^{-3} S^{-1}. [b] The pK_a values are for the straight-chain acids XCH_2CO_2H and are obtained from ref 20. [c] No reaction occurred in 24 h at rt. [d] The reaction is complete in less than 1 min under these conditions, and it was not possible to determine the absolute reaction rate.

reaction between the lactone and ethyl sodiomalonate was studied. Consumption of starting material was measured by either FTIR (change in intensity of lactone band) or GC (change in intensity of starting materials with respect to internal standards). The data was then placed into the first-order rate equation and the gradient of the line measured to give rate coefficients from which relative rates were determined (Table 2).

These results show that there is a strong correlation between the rate of reaction and the leaving group ability (pK_a) of the analogous straight-chain carboxylic acid[20] just as we had predicted (Table 2, entries 1−5). This is because the less basic the carboxylate (the more acidic the conjugate acid) the more the equilibrium is shifted from the lactone to the π-allyl intermediate (Scheme 7).

The rate of reaction of hydroxy lactone **4a** (Table 2, entry 6) is anomalous, and the high reactivity may be due to its ability to form a stabilized hydrogen-bonded intermediate that would further shift the equilibrium toward the π-allyl intermediate (Scheme 8). Increased reaction rates using trifluoroacetates (better leaving groups) compared to acetates have also been observed in acyclic π-allyl palladium chemistry.[21]

Scheme 7



Scheme 8

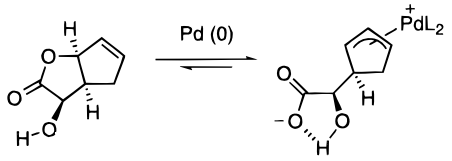
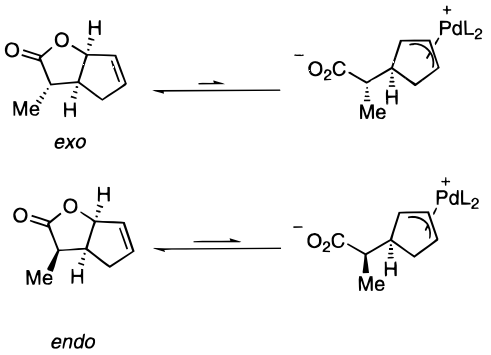


Table 3. Effect of *exo* and *endo* Substitution on Relative Reaction Rate[a]

lactones	k_{rel}
endo-methyl:*exo*-methyl **3a**:**3b**	>30:1[b]
endo-acetoxy:*exo*-acetoxy **10a**:**10b**	10.6:1
endo-azide:*exo*-azide **7a**:**7b**	6:1

[a] Reactions were conducted at 0.125 M concentration in THF using 1 mol % $Pd(PPh_3)_4$ as catalyst and 2 equiv of ethyl sodiomalonate. The reactions were followed by FTIR or GC as described in Table 2. [b] Reaction with **3a** was essentially instantaneous in refluxing THF but **3b** took about 15 min to go to completion under the same reaction conditions. No reaction occurred at rt.

Scheme 9



The effect of the stereochemistry of the C-4 substituent was determined, and the results are shown in Table 3. In all cases, the *endo* isomer reacted at a faster rate than the *exo* isomer. The higher reactivity of the *endo* isomers can be accounted for by consideration of the position of equilibrium between the lactones and their π-allyl palladium intermediates. In the case of the *endo* isomers, relief of steric compression will favor formation of the π-allyl intermediate, while less strain energy is released upon opening the *exo* isomer (Scheme 9). The larger the substituent, the greater the relief of steric compression in reaction of the *endo* isomer and the greater the difference in rates between the two diastereoisomers.

We have probed the scope and limitations of the palladium-catalyzed substitution reaction by reacting a

(20) Jencks, W. P.; Regenstein, J. *Handbook of Biochemistry*; Sober, H. A., Ed.; CRC Press: Boca Raton, 1970; J-150.

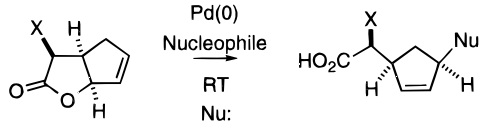
(21) Rajanbabu, T. V. *J. Org. Chem.* **1985**, *50*, 3642−3643. Stolle, A.; Salaun, J.; de Meijere, A. *Tetrahedron Lett.* **1990**, *31*, 4593−4596. Bernocchi, E.; Cacchi, S.; Morera, E.; Ortar, G. *Synlett* **1992**, 161.

Table 4. Yields (%) in Substition Reactions of a Range of Lactones with a Range of Nucleophiles

			nucleophile			
entry	lactone (X)	rel rate[a]	ethyl sodiomalonate	sodium benzenesulfinate	sodium azide	pyrrolidine
1	**4a** (OH)	>50	87	77	81	98
2	**7a** (N_3)	8.9	85	40[b]	79[c]	
3	**10a** (OAc)	3.1	83	80	81[c]	67[c]
4	**2** (H)	1	93	55[c]	30[c]	*d*

[a] Relative reactions rates with ethyl sodiomalonate from Table 2. [b] Product contaminated with benzenesulfonic acid. [c] Mixture of isomeric products obtained. Yield refers to combined yield of isomers. [d] Unidentified mixture of products obtained.

Scheme 10



range of lactones of differing activity with a range of nucleophiles (Scheme 10, Table 4). It was found that good yields of single diastereomers of products could be obtained either from reactions between highly active lactones (**4a**, Table 4, entry 1) and a range of nucleophiles or highly active nucleophiles (ethyl sodiomalonate) and a range of lactones. Reactions of slower reacting lactones with poorer nucleophiles gave rise to mixtures of isomers due to either palladium-mediated isomerization between *anti* and *syn* π-allyl palladium complexes or isomerization of the products.

Trost has recently studied the substitution reaction of allyl acetates with NaN_3 and observed concomitant isomerization of the product allyl azides.[16c] He found that using faster reacting allyl carbonates reduced the extent of isomerization significantly. The complete and clean reaction of NaN_3 with **4a** (Table 4, entry 1, single diastereomer formed) compared to **2** (Table 4, entry 4, mixture of diastereomers formed) is due to the increased reactivity of **4a** over **2**, which results from the increased stability of the corresponding carboxylate and the relief of steric compression. Both factors push the equilibrium between the π-allyl palladium intermediate and lactone toward the palladium complex.

Conclusion

A broad range of α-substituted lactones were prepared in order to study how electronic and steric factors influence the rate of substitution reactions. It was found that reaction rates increased with increasing electron-withdrawing ability of the substituent (X) and that there was a strong correlation between rate and pK_a of the corresponding substituted acetic acids (XCH_2CO_2H), with the exception of X = OH. The *endo*-hydroxy lactone reacted much faster than expected, probably because the intermediate hydroxy carboxylate can be stabilized by hydrogen bonding, providing a driving force for formation of the π-allyl palladium complex. However, the *exo*-hydroxy lactone reacted much more slowly than expected and gave rise to a mixture of products. We cannot satisfactorily account for this anamolous behavior. It was also found that the rates of reaction of the *endo* isomers were greater than the *exo* isomers. The increased rates can be accounted for by a shift in equilibrium from the lactone to the π-allyl palladium intermediate due to steric and electronic effects. Lactones with unactivated leaving groups such as **2** couple efficiently with good nucleophiles such as malonate but only poorly with less reactive nucleophiles such as azide. Lactones with activated leaving groups such as **4a** couple efficiently with a broad range of nucleophiles.

The availability of unsaturated lactones in enantiomerically pure form and the efficiency of reactions with a wide range of nucleophiles in a regio- and stereoselective manner provide a powerful method for the asymmetric synthesis of biologically interesting molecules.

Experimental Section

General Procedures. Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe, cannula, and septa techniques. Reagents purchased commercially were used without further purification. $Pd(PPh_3)_4$ was prepared according to Coulson's procedure.[22] Tetrahydrofuran was distilled from potassium/benzophenone ketyl. Solvents were dried using standard procedures.

4-*endo*-Methyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (3a) and 4-*exo*-Methyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (3b). To a solution of diisopropylamine (0.83 mL, 6 mmol) in THF (4 mL) cooled to −78 °C was added *n*-butyllithium (3.75 mL, 1.6 M in hexanes, 6 mmol). This solution was allowed to warm to 0 °C and was then held at this temperature for 15 min. The solution was then cooled to −78 °C. **2** (580 mg, 5 mmol) in THF (4 mL) was slowly added to the LDA solution. The solution was then stirred for 20 min at −78 °C. Iodomethane (680 μL, 2 mmol) was then added. The mixture was further stirred for 20 min before water was added (2 mL). The mixture was then allowed to warm to room temperature. Water was added and the reaction mixture extracted with ethyl acetate. The organic layers were combined and dried ($MgSO_4$). The solution was then passed through a short pad of Celite and condensed to give a mixture of *exo* and *endo methyl lactones* (92:8, **3b**:**3a**), which were separated by column chromatography using ethyl acetate:light petroleum (1:4) as eluent to give the *exo* lactone **3b** (526 mg 88%) as a colorless oil: IR (film) ν 2257, 1762 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.02 (1H, m), 5.81 (1H, m), 5.46 (1H, m), 2.72 (2H, m), 2.24 (2H, m), 1.22 (3H, d, J = 7.5 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 179.8, 136.0, 129.4, 87.3, 44.0, 41.9, 37.9, 15.7; MS *m*/*z* (EI) 138.068 67 (15) (M^+, $C_8H_{10}O_2$ requires 138.068 08), 94 (90), 79 (100).

Epimerization and Separation of 3a/3b. LDA was prepared as above, and then a mixture of *exo*- and *endo*-4-methyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (92:8, **3b**:**3a**) (690 mg, 5 mmol) in THF (4 mL) was slowly added. The mixture was stirred for 30 min before being quenched with saturated sodium sulfate solution (3 mL). The reaction mixture was then warmed to room temperature, extracted with dichloromethane, dried ($MgSO_4$), and condensed. Purification by column chromatography using ethyl acetate:light petroleum (1:4) as solvent furnished the *endo* compound **3a** (272 mg, 39%) as a colorless oil: IR (film) ν 2257, 1762 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.15 (1H, dt, J = 5.5, 2.0 Hz), 5.85 (1H, dt, J = 8.0, 2.0 Hz), 5.25 (1H, dt, J = 8.0, 2.2 Hz), 3.05 (1H, dq, J = 14.1, 10.3, 8.6 Hz), 2.85 (1H, dq, J = 14.2, 10.5, 7.0 Hz), 2.42 (2H, m), 1.15 (3H, d, J = 6.5 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 179.4, 139.4, 128.5, 86.8, 40.6, 37.5, 32.4, 12.3; MS *m*/*z* (EI) 138.068 67 (15) (M^+, $C_8H_{10}O_2$ requires 138.068 08), 79 (100).

4-*endo*-(Methanesulfonyl)-2-oxabicyclo[3.3.0]oct-7-en-3-one (5a). A solution of the hydroxy lactone **4a** (1.40 g, 10 mmol) in dichloromethane (30 mL) was cooled to 0 °C. Triethylamine (4 mL, 30 mmol) and methanesulfonyl chloride

(22) Coulson, D. *Inorg. Synth.* **1972**, *13*, 121−124.

(0.85 mL, 11 mmol) were added consecutively, and the mixture was stirred for 1 h. The solvent was then removed *in vacuo*, and the residue was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium chloride. The organic layers were combined, dried (sodium sulfate), and condensed. The crude product was filtered through a short pad of silica gel using ethyl acetate:petroleum ether (1:1) as eluent to give *the mesylate* **5a** (2.18 g, 100%) as a colorless viscous oil: IR (film) ν 2940, 1780, 1620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.26 (1H, dt, J = 2.0, 5.5 Hz), 5.94 (1H, dq, J = 2.0, 5.5 Hz), 5.50 (1H, d, J = 9.5 Hz), 5.40 (1H, dt, J = 2.0, 6.5 Hz), 3.36 (1H, m), 3.28 (3H, s), 2.72 (1H, m), 2.58 (1H, ddt, J = 2.0, 9.0, 18.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.1, 140.8, 127.6, 86.9, 75.4, 39.5, 31.9; MS *m*/*z* (CI) 219.0326 (15) ($M + H^+$, $C_8H_{11}O_5S$ requires 219.0327), 123 ($M - OSO_2CH_3$, 100), 78 (68), 67 (89).

4-*exo*-Bromo-2-oxabicyclo[3.3.0]oct-7-en-3-one (6a). The hydroxy lactone **4a** (2.80 g, 20 mmol) and triphenylphosphine (15.80 g, 60 mmol) were dissolved in anhydrous THF (250 mL) under nitrogen. Anhydrous zinc bromide (4.50 g, 20 mmol) and diethyl azodicarboxylate (DEAD) (9.40 mL, 60 mmol) were added at room temperature consecutively. The mixture was stirred at room temperature for 30 min and then was filtered through Celite. The solid residue was carefully washed with ethyl acetate and the filtrate condensed *in vacuo*. Purification by chromatography on silica gel using ethyl acetate:light petroleum (1:4) as eluent gave in the first fractions *the exo-bromo lactone* **6a** (2.43 g, 60%) as a white solid: mp 39.5−40.5 °C; IR (KBr disk) ν 3030, 2985, 1755 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.13 (1H, dt, J = 2.0, 5.5 Hz), 5.82 (1H, dq, J = 2.0, 5.5 Hz), 5.57 (1H, dt, J = 2.0, 7.0 Hz), 4.24 (1H, d, J = 4.5 Hz), 3.30 (1H, ddt, J = 4.5, 7.0, 9.0 Hz), 2.84 (1H, dddt, J = 1.0, 2.0, 9.0, 17.5 Hz), 2.39 (1H, ddt, J = 2.0, 7.0, 17.5 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.8, 138.0, 128.5, 87.9, 47.5, 43.4, 37.3; MS *m*/*z* (EI) 79 (100). Anal. Calcd for $C_7H_7BrO_2$: C, 41.41; H, 3.47; Br, 39.35. Found: C, 41.38; H, 3.27; Br, 39.30. In the later fractions the *endo* epimer **6b** (0.48 g, 12%) eluted as a colorless oil that solidified in the freezer: ν_{max} (film) 3060, 2945, 1770, 1620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.15 (1H, m), 5.88 (1H, m), 5.39 (1H, br d, J = 6.5 Hz), 4.84 (1H, d, J = 9.5 Hz), 3.31 (1H, m), 2.80−2.50 (2H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.6, 139.7, 127.8, 87.8, 44.9, 41.0, 37.0; MS *m*/*z* (EI) 204, 202 (M^+ < 1), 79 (100). Anal. Calcd for $C_7H_7BrO_2$: C, 41.41; H, 3.47; Br, 39.35. Found: C, 41.67; H, 3.59; Br, 39.05.

4-*endo*-Azido-2-oxabicyclo[3.3.0]oct-7-en-3-one (7a). Sodium azide (2.60 g, 40 mmol) was added to a solution of the *exo*-bromo lactone **6b** (4.06 g, 20 mmol) in DMSO (20 mL). The solution was stirred for 24 h at room temperature, diluted with ethyl acetate, and washed with brine. The organic layer was dried (Na_2SO_4) and condensed *in vacuo*. The crude product was purified by chromatography on silica gel using ethyl acetate:light petroleum (3:7) as eluent to give the *endo-azido lactone* **7a** (2.87 g, 87%) as a colorless oil: IR (film) ν 3060, 1770, 1620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.19 (1H, dt, J = 2.2, 5.5 Hz), 5.89 (1H, dq, J = 2.2, 5.5 Hz), 5.34 (1H, dt, J = 2.2, 6.5 Hz), 4.55 (1H, d, J = 9.5 Hz), 3.20 (1H, dddd, J = 6.0, 6.5, 9.0, 9.5 Hz), 2.64 (1H, ddt, J = 2.2, 6.0, 18.0 Hz), 2.48 (1H, ddt, J = 2.2, 9.0, 18.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.14, 140.29, 127.59, 86.99, 59.52, 39.45, 32.33; MS *m*/*z* (EI) 165 (M^+, 1), 137 ($M - N_2$, 100). Anal. Calcd for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 51.00; H, 4.39; N, 25.45.

4-*exo*-Azido-2-oxabicyclo[3.3.0]oct-7-en-3-one (7b). A procedure analogous to the one reported above was applied to the *endo-mesylate* **5a** to yield the *exo-azido lactone* **7b** (67%) as a colorless oil that crystallized on storage: mp 34−35 °C; IR (film) ν 3070, 1775, 1615 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.07 (1H, m), 5.87 (1H, m), 5.49 (1H, br d, J = 7.5 Hz), 3.95 (1H, d, J = 7.0 Hz), 2.90 (1H, dq, J = 1.5, 7.55 Hz), 2.76 (1H, ddq, J = 2.0, 7.5, 17.5 Hz), 2.47 (1H, d q, J = 2.0, 17.5 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.4, 136.7, 129.2, 87.7, 63.6, 42.5, 37.0. Anal. Calcd for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 51.10; H, 4.33; N, 25.15.

4-*endo*-Amino-2-oxabicyclo[3.3.0]oct-7-en-3-one (8a). Triphenylphosphine (4.73 g, 18 mmol) was added in small portions to a solution of the *endo*-azido lactone **7a** (2.97 g, 18 mmol) in tetrahydrofuran (18 mL), rapid evolution of nitrogen occurred. After complete reaction, water (1.62 g, 90 mmol) was added, and the mixture was stirred at room temperature for 24 h. After removal of the solvent, the crude product was purified by chromatography on silica gel (gradient of solvent ethyl acetate:methanol) to give the corresponding *endo-amino lactone* **8a** (2.30 g, 92%) as a pale yellow solid: mp 59−60 °C; IR (KBr disk) ν 1755, 1665, 1620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.13 (1H, dt, J = 2.2, 5.5 Hz), 5.85 (1H, dq, J = 2.2, 5.5 Hz), 5.21 (1H, dt, J = 2.2, 6.5 Hz), 3.95 (1H, d, J = 9.5 Hz), 3.06 (1H, tt, J = 6.5, 9.5 Hz), 2.49 (1H, ddt, J = 2.2, 6.5, 18.0 Hz), 2.37 (1H, ddt, J = 2.2, 9.5, 18.0 Hz), 1.72 (2H, br s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 178.3, 140.3, 128.2, 86.0, 53.2, 41.2, 31.3; MS *m*/*z* (EI) 95 (98), 94 (100). Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52, N, 10.06. Found: C, 60.16; H, 6.44; N, 9.81.

4-*exo*-Amino-2-oxabicyclo[3.3.0]oct-7-en-3-one (8b). A procedure analogous to the one reported above was applied to the *exo-azido lactone* to yield the *exo-amino lactone* **8b** (79%) as a pale yellow oil and 14% of its epimer **8a**. The epimers could not be separated by conventional chromatography, and the mixture was therefore used in the next step. The *exo* epimer showed: ^1H NMR (250 MHz, $CDCl_3$) δ 6.03 (1H, m), 5.85 (1H, m), 5.44 (1H, br d, J = 7.5 Hz), 3.27 (1H, d, J = 8.0 Hz), 2.85−2.63 (2H, m), 2.48 (1H, br d, J = 17.5 Hz), 1.51 (2H, br s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 178.9, 136.3, 129.3, 86.8, 57.8, 45.0, 37.1.

4-*endo*-[*N*-(benzyloxycarbonyl)amino]-2-oxabicyclo-[3.3.0]oct-7-en-3-one (9a). Sodium hydrogen carbonate (2.70 g, 32 mmol) and benzyl chloroformate (2.46 mL, 16 mmol) were added to a solution of the amino lactone **8a** (2.22 g, 16 mmol) in THF:H_2O (1:3, 64 mL) at 0 °C. The reaction was allowed to warm to room temperature (1 h) and was quenched with an aqueous saturated ammonium chloride solution. The reaction mixture was extracted with ethyl acetate, and the combined organic layers were dried (Na_2SO_4) and condensed *in vacuo*. Filtration of the crude product through silica gel using ethyl acetate:light petroleum (3:7) as eluent gave *the carbamate* **9a** (4.11 g, 94%) as a white solid: mp 146−147 °C; IR (KBr disk) ν 3320, 1770, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 220 K, too broad at 293 K) δ 7.37 (5H, br s), 6.22 (1H, dt, J = 2.2, 5.5 Hz), 5.97 (1H, d, J = 6.0 Hz), 5.92 (1H, dq, J = 2.2, 5.5 Hz), 5.33 (1H, dt, J = 2.2, 6.0 Hz), 5.07 (2H, AB, J = 11.0 Hz), 4.78 (1H, dd, J = 6.0, 9.0 Hz), 3.37 (1H, tt, J = 6.0, 9.0 Hz), 2.46 (1H, ddt, J = 2.2, 9.0, 18.0 Hz), 2.34 (1H, ddt, J = 2.2, 6.0, 18.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.1, 156.2, 140.7, 136.0, 128.6, 128.3, 128.1, 127.9, 87.0, 67.4, 53.7, 40.5, 32.0; MS *m*/*z* (EI) 274 ($M + H^+$, 1), 167 ($M - PhCH_2O$, 85), 107 (100). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.81; H, 5.40; N, 5.04.

4-*exo*-[*N*-(benzyloxycarbonyl)amino]-2-oxabicyclo[3.3.0]-oct-7-en-3-one (9b). A procedure analogous to the one reported above was applied to the *endo*-amino lactone (contaminated with its C-4 epimer). The *exo-carbamate* **9b** was purified by chromatography on silica gel using ethyl acetate: light petroleum (3:7) as eluent to yield a colorless oil (77%): IR (film) ν 3340, 1780, 1730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.25 (5H, br s), 5.95 (1H, br s), 5.89 (1H, d, J = 7.5 Hz), 5.74 (1H, br s), 5.41 (1H, br d, J = 7.0 Hz), 5.00 (2H, s), 3.91 (1H, t, J = 8.0 Hz), 3.00 (1H, br s), 2.55 (2H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 175.2, 156.4, 136.5, 136.0, 129.1, 128.6, 128.3, 128.2, 87.5, 67.3, 53.4, 43.1, 37.2; MS *m*/*z* (CI) 274.1071 (67) ($M + H^+$, $C_{15}H_{16}NO_4$ requires 274.1079), 213 (53).

General Procedure for the Substitution of Lactones 4a/b, 6a/b−7a/b, and 9a/b−10a/b by Ethyl Sodiomalonate. To a solution of lactone (1 mmol) in THF (1 mL) was added $Pd(PPh_3)_4$ (60 mg, 0.05 mmol). The mixture was stirred at the room temperature until complete solution had occurred. A 2 M THF solution of diethyl sodiomalonate prepared by addition of sodium hydride (80% in oil) (60 mg, 2 mmol) to diethyl malonate (0.333 mL, 2.2 mmol) in THF (1 mL) was added. The reaction mixture was stirred for 10 min (reaction time of slowest observed reaction) at the appropriate temperature and then diluted with ethyl acetate and extracted with a saturated aqueous solution of sodium bicarbonate (3 × 10 mL). The combined aqueous layers were washed with ethyl

acetate (3 × 10 mL), acidified (HCl) to pH 1, and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and then dried (Na_2SO_4). The solvent was then removed *in vacuo* to give the corresponding acid as a colorless oil.

(1′*S*,*R*,4′*S*,*R*)-2-[4′-(Dicarbethoxymethyl)cyclopent-2′-enyl]ethanoic Acid from Compound 2. The acid was obtained as a colorless oil (93%): IR (film) ν 3600−2400, 1730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.72 (2H, m), 4.18 (4H, q, J = 7.0 Hz), 3.35 (1H, m), 3.23 (1H, d, J = 9.0 Hz), 3.10 (1H, m), 2.53−2.29 (3H, m), 1.25 (6H, t, J = 7.0 Hz), 1.18 (1H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 178.6, 168.5, 135.1, 132.5, 61.3, 57.2, 45.1, 41.4, 40.4, 34.8, 14.0; MS *m*/*z* (EI) 284.1264 (13) (M, $C_{14}H_{20}O_6$ requires 284.1260), 224 (85).

(2*S*,*R*,1′*S*,*R*,4′*R*,*S*)-2-Methyl-2-[4′-(dicarbethoxymethyl)cyclopent-2′-enyl]ethanoic Acid from Compound 3a. This reaction was conducted at reflux. The acid was obtained as a colorless oil (87%): IR ($CDCl_3$) ν 2980, 2225, 1722 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.70 (2H, m), 4.19 (4H, q, J = 8.0, 15.0 Hz), 3.32 (1H, m), 3.22 (1H, d, J = 9.5 Hz), 2.95 (1H, m), 2.85 (2H, m), 1.24 (7H, t, J = 8.5, 15.0 Hz), 1.17 (3H, d, J = 7.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 181.9, 168.5, 133.2, 61.4, 57.2, 47.9, 44.9, 44.1, 33.0, 14.8, 14.1; MS *m*/*z* (EI) 298.141 05 (2.5) (M^+, $C_{15}H_{22}O_6$ requires 298.141 63) 225 (95), 51 (100).

Substitution Reactions of Lactones 4a, 10a, 7a, and 2 with Nucleophiles Other Than Malonate. To a solution of the lactone (1 mmol) in THF (2 mL) was added $Pd(PPh_3)_4$ (60 mg, 0.05 mmol). The mixture was stirred at room temperature until complete solution had occurred. Two equiv of the nucleophile was dissolved in the appropriate solvent (1 mL) and was then added to the reaction mixture. The reaction mixture was then left to stir for 1.5 h. The reaction was then poured into hydrochloric acid (5 mL, 2 M), extracted with ethyl acetate, and dried with magnesium sulfate before being concentrated under reduced pressure to give the crude acid derivative.

(2*S*,*R*,1′*R*,*S*,4′*S*,*R*)-2-Hydroxy-2-(1′-azidocyclopent-2′-enyl)ethanoic Acid (4a with NaN_3). The reaction was performed using a solution of sodium azide (2 mmol) in water (1 ml). The acid **15** was obtained as a colorless oil (81%): IR (film) ν 3500−2400, 1750 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.90 (2H, s), 4.45 (1H, m), 4.20 (1H, d, J = 5.0 Hz), 3.15 (1H, m), 2.55 (1H, ddd, J = 8.0, 9.0, 15.0 Hz), 1.85 (1H, dt, J = 5.0, 15.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.4, 133.9, 132.6, 72.0, 66.3, 48.5, 32.6; MS *m*/*z* (FAB) 184.0722 (0.4) ($M^+ + H^+$, $C_7H_{10}O_3N_3$ requires 184.0728), 123 (100).

(2*S*,*R*,1′*R*,*S*,4′*S*,*R*)-2-Hydroxy-2-[1′-(phenylsulfonyl)cyclopent-2′-enyl]ethanoic Acid (4a with Sodium Benzenesulfinate). The reaction was performed using sodium benzenesulfinate (1 mmol). Recrystallization of the crude product from $CDCl_3$ yielded the corresponding acid **16** as a white solid (82%): mp 78−82 °C; IR (KBr) ν 1725, 1695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.80 (2H, m), 7.75 (1H, m), 7.60 (2H, m), 6.00 (1H, d, J = 5.0 Hz), 5.70 (1H, d, J = 5.0 Hz), 4.35 (1H, m), 4.25 (1H, d, J = 4.0 Hz), 3.50 (1H, m), 2.50 (1H, dt, J = 9.0, 15.0 Hz), 2.30 (1H, dt, J = 6.5, 15.0 Hz); ^{13}C NMR (63 MHz, CD_3OD) δ 176.4, 140.7, 138.8, 135.2, 130.4, 130.2, 126.2, 74.2, 73.1, 50.9, 27.4; MS *m*/*z* (FAB) 283.0647 (60) ($M^+ + H^+$, $C_{13}H_{15}O_5S$ requires 283.0640), 279 (100).

(2*S*,*R*,1′*R*,*S*,4′*S*,*R*)-2-Hydroxy-2-(1′-pyrrolidylcyclopent-2′-enyl)ethanoic Acid (4a with Pyrrolidine). The reaction was performed using pyrrolidine (2 mmol). The excess pyrrolidine was then removed *in vacuo* to yield a crude white solid. Purification by flash chromatography on silica gel eluting with methanol:dichloromethane (2:8) yielded the corresponding acid **17** as a light brown oil (209 mg, 99%): IR (film) ν 3500−3000, 1600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.90 (1H, d, J = 6.0, 5.75 Hz), (1H, d, J = 6.0 Hz), 4.05 (1H, br m), 3.90 (1H, d, J = 5.0 Hz), 3.18 (1H, br m), 3.10−2.90 (4H, m), 2.30 (1H, dt, J = 6.0, 11.0 Hz), 1.85 (5H, br m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 178.6, 138.9, 128.1, 73.1, 68.8, 50.1, 49.3, 44.6, 23.8; MS *m*/*z* (FAB) 212.1291 (100) (M + H^+, $C_{11}H_{17}O_3N$ requires 212.1286), 166 (17).

2-Acetoxy-2-(4-sulfonylpent-2-enyl)ethanoic Acid (10a with Sodium Benzenesulfinate). The reaction was performed using 1 equiv of sodium benzenesulfinate. The crude oil was purified by flash chromatography on silica gel using pure ethyl acetate as eluent. This yielded the *sulfone acetoxy acid* as a colorless oil (268 mg, 82%): IR (film) ν 3049, 1741 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.85 (2H, m), 7.5 (3H, m), 5.95 (1H, m), 5.7 (1H, m), 4.55 (1H, d, J = 6 Hz), 4.25 (1H, m), 3.25 (1H, m), 2.3 (1H, dt, J = 14, 8, 8 Hz), 2.1 (1H, dt, J = 14, 5, 5 Hz), 2.0 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.6, 170.0, 137.6, 137.0, 134.1, 129.2, 129.0, 126.3, 73.5, 71.7, 46.8, 26.1, 20.7; MS *m*/*z* (FAB) 325.074 395 (65) (M + H^+, $C_{15}H_{17}O_6S$ requires 325.074 585), 307 (100).

Reaction of 10a with Sodium Azide. Lactone **10a** (1 mmol) in THF (2 mL) was reacted with sodium azide (130 mg, 2 mmol) in water (1 mL) following the procedure given above but stirred for 2 days. Purification by base/acid wash gave a 2:1 mixture of diasteromeric *azido acetates* as a colorless oil (200 mg, 81%): ^1H NMR (250 MHz, $CDCl_3$) δ 5.95 (0.66H, m), 5.90 (1.33H, m), 4.95 (0.33H, d, J = 5.0 Hz), 4.85 (0.66H, d, J = 5.0 Hz), 4.40 (1H, m), 3.37 (1H, m), 2.75−2.20 (2H, m), 2.10 (1H, s), 2.05 (2H, s).

Reaction of 10a with Pyrrolidine. Lactone **10a** (1 mmol) was reacted with pyrrolidine (193 μL, 4 mmol) following the procedure given above but stirred for 2 days. Evaporation of the pyrrolidine followed by filtration through silica gel (EtOAc) gave a 3:2 diasteromeric mixture of *amines* as a colorless oil (151 mg, 67%): ^1H NMR (250 MHz, $CDCl_3$) δ 6.10−5.6 (2H, m), 4.45 (0.4H, d, J = 4.5 Hz), 4.40 (0.6H, d, J = 4.5 Hz), 3.7−3.25 (4H, m), 3.25−2.40 (4H, m), 2.05 (1.8H, s), 2.00 (1.2H, s), 2.05−1.5 (4H, m).

Reaction of 7a with Sodium Benzenesulfinate. Lactone **7a** (1 mmol) was reacted with sodium benzenesulfinate (656 mg, 4 mmol) following the procedure given above but stirred for 2 days. Purification by base/acid wash gave the *azido sulfone* as a white solid (131 mg, 40%). Further purification by chromatography was not possible due to extensive decomposition: ^1H NMR (250 MHz, $CDCl_3$) δ 7.80−7.50 (5H, m), 5.95 (1H, m), 5.40 (1H, m), 4.25 (1H, m), 3.40 (1H, d, J = 5.5 Hz), 3.05 (1H, m), 2.25 (1H, m), 2.01 (1H, m).

Reaction of 7a with Sodium Azide. Lactone **7a** (1 mmol) in THF (2 mL) was reacted with sodium azide (130 mg, 2 mmol) in water (1 mL) following the procedure given above but stirred for 2 days. Purification by base/acid wash gave a 1:1 diasteromeric mixture of *azido azides* as a colorless oil (194 mg, 79%). The mixture is heat sensitive and best handled in solution: ^1H NMR (250 MHz, $CDCl_3$) δ 6.20−5.40 (2H, m), 4.40 (1H, m), 4.00 (0.5H, d, J = 5.1 Hz), 3.90 (0.5H, d, J = 5.1 Hz), 3.5−1.6 (3H, m).

Reaction of 2 with Sodium Benzenesulfinate. Lactone **2** (1 mmol) was reacted with sodium benzenesulfinate (328 mg, 2 mmol) following the procedure given above but refluxed for 24 h. Evaporation of solvent gave a 3:1 diasteromeric mixture of *sulfones* as a white solid: ^1H NMR (250 MHz, $CDCl_3$) δ 7.85−7.30 (5H, m), 6.05 (1H, m), 5.70 (1H, m), 4.30 (0.75H, m), 4.05 (0.25H, m), 3.25−1.75 (5H, m).

Reaction of 2 with Sodium Azide. Lactone **2** (1 mmol) in THF (2 mL) was reacted with sodium azide (130 mg, 2 mmol) in water (1 mL). The mixture was refluxed for 24 h and then purified by base/acid wash to furnish a 3:7 diasteromeric mixture of *azides* (55 mg, 30%) as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 6.20 (0.28H, m), 6.0 (0.72H, m), 5.8 (0.28H, m), 5.40 (0.72H, m), 4.30 (1H, m, br), 3.05 (0.77H, m, br), 2.00−2.80 (3.3H, m, br), 1.45 (1H, m).

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Supporting Information Available: Copies of ^{13}C NMR spectra of all compounds except **6a**/**b**−**9a**/**b** and data for the substitution reactions of lactones **3b**, **4a**/**b**, **6a**/**b**, **7a**/**b**, **9a**/**b**, and **10a**/**b** with ethyl sodiomalonate and the substitution reactions of lactones **2** and **7a** with NaN_3 and $NaSO_2Ph$ (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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